Chromosome 11p15.5 Regional Imprinting: Comparative Analysis of KIP2 and H19 in Human Tissues and Wilms' Tumors

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Genomic imprinting leads to parent-of-origin-dependent gene silencing with monoallelic RNA expression in tissues of the offspring. In the region of human chromosome 11p15.5, which is associated with the Beckwith-Weidermann syndrome (BWS) and is subject to recurrent maternal loss of heterozygosity (LOH) in embryonal tumors such as Wilms' tumor (WT) and embryonal rhabdomyosarcoma (RMS), there are two well-studied imprinted genes: H19, which is paternally imprinted, and IGF2, which is silenced on the maternal allele. Recently, the human KIP2 gene, which encodes a cyclin-cdk inhibitor and which has been proposed as a candidate tumor suppressor gene, has been localized centromeric to IGF2 and close to the positions of several chromosomal translocation breakpoints in kindreds with BWS.

Recent observations have suggested the existence of chromosomal domains containing clusters of imprinted genes which could have important implications both for the mechanism of imprinting and for the mode of disregulation of imprinted genes in human diseases. To test the possibility of coordinate disruption of imprinting of multiple 11p15.5 genes in these tumors, we have characterized total and allele-specific mRNA expression levels via Northern analysis and DNA methylation by Southern blotting of the 11p15.5 KIP2 gene in normal human tissues, WTs and RMS.

Both KIP2 alleles are expressed, but there is a bias with the maternal allele contributing 70-90% of mRNA which suggests the presence of one or more paternally imprinted tumor suppression genes in this chromosomal region. Tumors with LOH show moderate to marked reductions in KIP2 mRNA relative to control tissues, and residual mRNA expression is from the imprinted paternal allele. Among WTs without LOH, most cases with H19 inactivation also have reduced KIP2

expression and most cases with persisent H19 expression have high levels of KIP2 mRNA. In contrast to the extensive hypermethylation of the imprinted H19 allele, both KIP2 alleles are hypomethylated and WTs with biallelic H19 hypermethylation lack comparable hypermethylation of KIP2 DNA. 5-aza-2'-deoxycytidine (aza-C), a demethylating drug which has been widely used as a probe for the methylation-dependence of expression of imprinted genes, increases H19 expression in RD RMS cells but does not activate KIP2 expression.

These data indicate coordinately reduced expression of two linked paternally imprinted genes in most WTs and also suggest mechanistic differences in the maintenance of imprinting at these two loci. In conclusion, it appears that WTs formation is increasingly likely to be promoted by the aberrant expression of multiple imprinted genes in an extended domain of chromosome 11p15.5 with a bipaternal epigenotype not only in the cases with LOH, but also in about half of the cases which retain heterozygosity. (*Human Molecular Genetics, 1996, vol5, No 8*)

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ARTICLE

Three Tumor-Suppressor Regions on Chromosome 11p Identified by High-Resolution Deletion Mapping in Human Non-Small-Cell Lung Cancer

G Bepler and MA Garcia-Blanco

Non-small-cell lung cancer is the leading cause of cancer death for men and women in the industrialized nations. Identification of regions for genes involved in its pathogenesis has been difficult. Data presented here show three distinct regions identified on chromosome 11p. Two regions on 11p13 distal to the Wilms tumor gene WT1 and on 11p15.5 between the markers HBB and D11S860 are described. The third region on the telomere of 11p15.5 has been previously described and is further delineated in this communication. By high-resolution mapping the size of each of these regions was estimated to be 2-3 megabases. The frequency of somatic loss of genetic information in these regions (57%, 71%, and 45%, respectively) was comparable to that seen in heritable tumors such as Wilms tumor (55%) and retinoblastoma (70%) and suggests their involvement in pathogenesis of non-small-cell lung cancer. Gene dosage analyses revealed duplication of the remaining allele in the majority of cases in the 11p13 and the proximal 11p15.5 region but rarely in the distal 11p15.5 region. In tumors with loss of heterozygosity in all three regions any combination of duplication or simple deletion was observed, suggesting that loss of heterozygosity occurs independently and perhaps at different points in time. These results provide a basis for studies directed at cloning potential tumor-suppressor genes in these regions and for assessing their biological and clinical significance in non-small-cell lung cancer.

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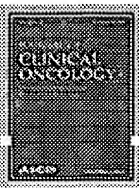

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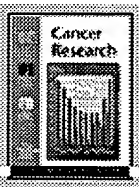

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